REMARKS

Rejection of claims 1-23 under 35 U.S.C. § 112, first paragraph

Claims 1-23 were rejected for failure to satisfy the written description requirement with regard to the recitation of *Streptococcus pneumoniae* serotypes/serogroups. For the following reasons, the applicant respectfully disagrees.

The Written Description Guidelines (Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, "Written Description" Requirement, 66 Fed. Reg. 1099 (2001)) states at page 1106, col.1, "The description need only describe in detail that which is new or not conventional." The *Streptococcus pneumoniae* serotypes/serogroups and their polysaccharides are not new or non-conventional. Rather, they are well known and ready available to those of ordinary skill in the art. This is clear from the specification, which notes, for example (a) at page 2, ln. 24 *et seq.*, a Finnish study in the 1980s, which identified 8 serogroups/serotypes responsible for 90% of invasive infections (serogroups/serotypes 4, 6, 7, 9, 14, 18, 19, and 23), (b) at p. 3, ln. 6 *et seq.*, that a commercially available pneumococcal vaccine containing polysaccharides of 23 serotypes was commercially available, and (c) throughout the specification numerous serotypes/serogroups are specifically identified by their commonly accepted designation (*e.g.*, 6B, 7F, 9V, 18C, 19F, 23F, etc.). Furthermore, U.S. 5,623,057 (being applied against the present claims in the § 103 rejections), notes that *Streptococcus pneumoniae* have been subdivided into 84 serotypes based on their capsular polysaccharides These disclosures thus manifest that the *Streptococcus pneumoniae* serotypes/serogroups and their polysaccharides were well known in the art and that the applicant was well aware of this fact. Accordingly, as stated in the Written Description Guidelines, the specification need not describe the various serotypes/serogroups.

The claimed invention is directed to a composition comprising a plurality of different conjugates comprised of polysaccharides derived from *Streptococcus pneumoniae* and at least two different protein carriers. The specification makes clear that the invention can employ *any* one or more polysaccharides derived from any *Streptococcus pneumoniae* serotypes/serogroups, although certain serotypes, being responsible for the majority of infections, are preferred. The applicant respectfully submits that one of ordinary skill in the art at the time of filing the present application would appreciate that, given the well known nature of the multiple *Streptococcus pneumoniae* serotypes/serogroups and the previous use in vaccine compositions of their polysaccharides, alone

and in conjugates, the applicant had in his possession a composition comprising two or more of these polysaccharides and two or more protein carriers in the form of polysaccharide-protein conjugates. Consequently, the applicant respectfully requests reconsideration and withdrawal of this rejection.

Rejection of claims 1-23 under 35 U.S.C. § 112, second paragraph

Claims 1-23 were rejected as indefinite in the recitation of "n" conjugates, the Office Action questioning "which conjugates of *Streptococcus* is the applicant claiming and exactly how many does "n" encompass." For the following reasons, the applicant respectfully traverses.

The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. *E.g., Miles Laboratories Inc. v. Shandon Inc.*, 27 USPQ2d 1123, 1126 (Fed. Cir. 1993). With regard to the inquiry as to exactly how many "n" encompasses, claim 1 states "'n' is a number equal to or greater than 2." The applicant respectfully submits that one of ordinary skill in the art would be able to determine where a number is equal to or greater than 2 and thereby determine the bounds of this limitation. This is sufficient to satisfy the legal requirements for definiteness.

With regard to the inquiry as to which conjugates of *Streptococcus* the applicant is claiming, it is noted that the claims encompass *compositions* comprising two or more conjugates comprising *any Streptococcus* polysaccharide and *any* carrier protein, provided that there are at least two conjugates in the composition having different carrier proteins. The applicants respectfully submit that this is clear from claim 1, which includes no limitations as to which *Streptococcus* polysaccharides or which carrier proteins are employed in the recited conjugates.

In addition, however, the ordinary artisan knowing the nature of the conjugates in any particular composition would be able to instantly determine whether the composition contains two or more conjugates with at least one *Streptococcus* polysaccharide and two different proteins, *i.e.*, she would be able to determine whether that composition fell within the scope of the present claims. Thus, the legal requirement for definiteness are satisfied.

Claims 1 and 14 were rejected as indefinite in the recitation of the word "especially." Claim 1, however, does not recite this term. The term has been deleted in claim 14 and new claim 24 drawn to the embodiment comprising 12 to 22 conjugates.

Lastly, the Office Action alleged that claims 1-23 were vague and indefinite in the recitation of "derived" from *Streptococcus pneumoniae*, stating that, for example, "derived from may encompass unknown modifications to the protein [sic, polysaccharide?]." The applicant respectfully disagrees.

The applicants respectfully submit that the phrase "a polysaccharide . . .derived from a *Streptococcus pneumoniae* serotype/serogroup" would be clear to one skilled in the art in view of the specification and common usage in the art. For example, page 10 of the specification discusses polysaccharides derived from a number of different serotypes (lns. 5-7) and states that the polysaccharides can be employed in crude form after extraction/purification (lns. 29-30) or can be fragmented in art recognized ways (lns. 30-35). At page 12, lns. 16-22, the specification teaches that in order to effect coupling to the carrier protein, the polysaccharide can be reductively animated. Indeed, chemical modifications are discussed on page 12 in which the specification describes the product as "the polysaccharide thus derived."

Furthermore, several U.S. patents claim compositions employing the phrase "polysaccharide derived from" without defining the phrase within the document:

1. U.S. 5,623,057 (on which the Office Action relies to reject the claims as obvious) recites the phrase "**polysaccharide derived** from one or more subtypes of *Streptococcus pneumoniae*" in claim 1.
2. U.S. 5,795,580 claims "An antigenic conjugate molecule comprising a type V capsular **polysaccharide derived** from a Group B streptococcus bacteria and a protein component . . . in claim 1.
3. U.S. 5,565,204 claims "An immunogenic polysaccharide-protein conjugate obtained by reductive amination comprising (a) an oxidized **polysaccharide derived** from the capsular polysaccharide of Streptococcal pneumoniae (S. pneumoniae), and (b) the pneumolysin protein of *S. pneumoniae* . . . ."
4. U.S. 5,371,197 claims "A covalent protein-dimeric polysaccharide conjugate immunogen wherein ... the **polysaccharides are derived** from the group of bacteria selected from Haemophilus influenzae b, Streptococcus pneumoniae subtype 1, 2, 3, 4, 5, 6 A, 6 B, 7 F, 8, 9 N, 9 V, 10 A, 11 A, 12 F, 14, 15 B, 17 F, 18 C, 19 A, 19 F, 20, 22 F, 23 F, 33 F."

Significantly, each of these patents employs the term as applied to *S. pneumoniae* polysaccharides, as recited in the present. Many additional U.S. patents employ the phrase in relation to other types

of polysaccharides. This is further evidence that the term is commonly employed and understood by those skilled in the art. This also manifests the Patent Office's recognition of this fact and the consequent implication that the term is sufficiently definite to satisfy the requirements of § 112.

In view of the foregoing, therefore, the applicant respectfully requests reconsideration and withdrawal of this rejection.

Rejection of claims 1-9 and 12-15 under 35 U.S.C. § 103(a)

The claims were rejected as obvious over Marburg *et al.* (U.S. 5,623,057), which teaches a *S. pneumoniae* polysaccharide-protein conjugate, in view of Matuhasi *et al.* (U.S. 4,372,883), which teaches Tt and Dt proteins used in polysaccharide-protein conjugates illicit a strong immune response. The Office Action reasoned that while Marburg *et al.* does not teach a conjugate composition comprising capsular polysaccharide from *Streptococcus pneumoniae* linked to more than one immunogenic carrier protein, one of ordinary skill in the art would have (a) been motivated to make such a composition in view of the teachings of Matuhashi *et al.*, and (b) had a reasonable expectation that incorporation of an additional carrier protein would boost the immunological response. For the following reasons, the applicant respectfully disagrees.

The applicant disagrees with conclusion that one skilled in the art would be motivated to employ multiple protein carriers to boost an immune response with a reasonable expectation of success. The Office Action fails to indicate to what the immune response would be boosted. To the polysaccharide? To the carrier protein? Furthermore, because of the phenomenon of antigenic competition, one skilled in the are could not have a reasonable expectation that merely adding a second immunogenic protein to a composition comprising a first would result in boosting of the immunogenic response to the first. Indeed, it would not be unexpected that adding another antigen would depress the immune response to the first antigen.

In this regard, the Patent Office's attention is also directed to Wuorimaa *et al.*, *Vaccine* **19**, 1863 (2001) ("Wuorimaa *Vaccine*"); Wuorimaa *et al.*, *Ped. Infect. Dis. J.* **20**, 272 (2001) ("Wuorimaa *PIDJ*"); Dogan *et al.*, *Infect. Immun.* **66**, 2093 (1998); Åhman *et al.*, *Vaccine* **17**, 2726 (1999); and Fattom *et al.*, *Vaccine* **17**, 126 (1999) (copies of these references are enclosed with this filing). Each of these references was published after the priority date of the present application but manifest that even at that time there was uncertainty as to the affects on immunological response to

increased vaccine valency. For example, Wuorimaa *PIDJ* states in the last paragraph that "[t]he increase in valency may decrease immunogenicity because of carrier-mediated influence" (although such an effect was not observed with the multi-valent -conjugate vaccine studied). Dagan *et al.*, Fattom *et al.*, and Åhman *et al.* all relate to the phenomenon of epitopic overload. For Example, in the abstract, Fattom *et al.* states, "The combination of [capsular polysaccharide] conjugate vaccines into a single multivalent injection may result in competition among the different components and adversely affect the immunogenicity of any individual conjugate." These post-filing publications manifest that one skilled in the art could not have had a reasonable expectation of success.

Furthermore, the claimed compositions have a property not suggested by the prior art. As the applicants observed (specification p. 3, ln. 20, to p. 4, ln. 9), the use of a *S. pneumococcus* polysaccharide-Dt (or Tt) conjugate resulted in negative interference on the induction of anti-HiB antibodies. Unlike prior art compositions, the applicants compositions do not cause this effect yet still maintain the same degree of *S. pneumococcus* immunogenicity. This property is nowhere suggested by the cited art. And as a composition and all of its properties cannot be separated (*In re Papesch*, 137 USPQ 43 (C.C.P.A. 1963)), the failure of the prior art to recognize or suggest this prior means the presently claimed compositions cannot be obvious.

In view of the foregoing, therefore, the applicant respectfully requests reconsideration and withdrawal of this obviousness rejection.

Rejection of claims 1, 8-11, and 16-23 under 35 U.S.C. § 103(a)

Claims 1, 8-11, and 16-23 were rejected as obvious over Marburg *et al.* and Matuhashi *et al.*, in view of Peeters *et al.* for the previous reasons in view of Peeters *et al.*'s teaching of a dosage of less than 50 µg/dose. The applicant respectfully traverse.

Peeters *et al.* fails to compensate for the deficiencies of Marburg *et al.* and Matuhashi *et al.*, described above. That is, none of Marburg *et al.*, Matuhashi *et al.*, or Peeters *et al.*, alone or in combination, suggest compositions of conjugates of *S. pneumococcus* polysaccharide(s) and proteins, wherein at least two different proteins are employed. Nor do any of these references, alone or in combination, suggest that such compositions would not have a negative effect on antibody production observed in prior art compositions.

In view of the foregoing, therefore, the applicant respectfully requests reconsideration and withdrawal of this obviousness rejection.

If there are any questions or comments regarding this Response or application, the Examiner is encouraged to contact the undersigned attorney as indicated below.

Respectfully submitted,

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APPLICATION SERIAL NO. 09/423,698

New Redlined Version Of Claims

1. (Amended) A composition comprising "n" conjugates C1 to Cn, wherein
   (a) each conjugate comprises
   (i) a polysaccharide S1 to Sn derived from a *Streptococcus pneumoniae* serotype/serogroup, respectively, and
   (ii) a carrier protein P1 to Pn, respectively;
   (b) "n" is a number equal to or greater than 2;
   (c) the polysaccharides S1 to Sn are identical or there are from 2 to "n" different polysaccharides; and
   (d) the carrier proteins P1 to Pn are selected independently from a group consisting of "m" carrier proteins A1 to Am, wherein "m" is a number equal to or greater than 2;
   (e) provided that at least one of the carrier proteins P1 to Pn is different from the others.

2. (Amended) The composition according to Claim 1, in which the conjugates C1 to Cn are all different from each other either by their polysaccharide, by their carrier protein, or by their polysaccharide and their carrier protein.

3. (Amended) The composition according to Claim 2, in which the polysaccharides S1 to Sn are all different from each other.

5. (Amended) The composition according to Claim 4, in which "n" is a number equal to or greater than 10.

7. (Amended) The composition according to Claim 6, in which when "n" is an even number, "n"/2 carrier proteins P1 to Pn are A1 and "n"/2 carrier proteins P1 to Pn are A2 or when "n" is an odd number, ("n"+1)/2carrier proteins P1 to Pn are A1 and ("n"-1)/2 carrier proteins P1 to Pn are A2.

9. (Amended) The composition according to Claim 8, in which the carrier proteins P1 to Pn are selected from the group consisting of Dt and Tt.

12. (Amended) The composition according to Claim 1, which comprises 10 or 11 valences represented by 10 or 11 conjugates in which the polysaccharides are all different from each other and are derived from the serotypes chosen from serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F of *S. pneumoniae.*

13. (Amended) The composition according to Claim 12, which comprises 10 or 11 conjugates selected from:

- serotype 1 polysaccharide coupled to Tt or to Dt;
- serotype 3 polysaccharide coupled to Dt;
- serotype 4 polysaccharide coupled to Tt;
- serotype 5 polysaccharide coupled to Tt or to Dt;
- serotype 6B polysaccharide coupled to Dt;
- serotype 7F polysaccharide coupled to Tt or to Dt;
- serotype 9V polysaccharide coupled to Tt;
- serotype 14 polysaccharide coupled to Dt;
- serotype 18C polysaccharide coupled to Dt;
- serotype 19F polysaccharide coupled to Tt; and
- serotype 23F polysaccharide coupled to Tt.

14. (Amended) The composition according to Claim 1that comprises 10 or 11 different polysaccharides and 12 to 22 conjugates, in which the polysaccharides are derived from the serotypes chosen from serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F and in which conjugates having the same polysaccharide differ from each other in the carrier protein.

15. (Amended) The composition according to Claim 14, which comprises:

- serotype 1 polysaccharide coupled to Tt;
- serotype 3 polysaccharide coupled to Dt;
- serotype 4 polysaccharide coupled to Tt;
- serotype 5 polysaccharide coupled to Tt;

- serotype 6B polysaccharide coupled to Dt;
- serotype 6B polysaccharide coupled to Tt;
- serotype 7F polysaccharide coupled to Tt;
- serotype 9V polysaccharide coupled to Tt;
- serotype 9V polysaccharide coupled to Dt;
- serotype 14 polysaccharide coupled to Dt;
- serotype 18C polysaccharide coupled to Dt;
- serotype 18C polysaccharide coupled to Tt;
- serotype 19F polysaccharide coupled to Tt;
- serotype 23F polysaccharide coupled to Tt; and
- serotype 23F polysaccharide coupled to Dt.

16. (Amended) A composition that comprises "n" conjugates C1 to Cn, wherein

(a) each conjugate comprises

(i) a polysaccharide S1 to Sn, respectively, and

(ii) a carrier protein P1 to Pn, respectively,

(b) "n" is a number equal to or greater than 2;

(c) the polysaccharides S1 to Sn are identical or there are from 2 to "n" different polysaccharides; and

(d) the carrier proteins P1 to Pn are selected independently from a group consisting of diphtheria (Dt) and tetanus (Tt) toxoids,

(e) provided that at least one of the carrier proteins P1 to Pn is different from the others and the quantity of Dt is less than or equal to 200 and the quantity of Tt is less than or equal to 50 µg/dose.

17. (Amended) The composition according to Claim 16, in which the conjugates C1 to Cn are all different from each other either by their polysaccharide, by their carrier protein, or by their polysaccharide and their carrier protein.

18. (Amended) The composition according to Claim 17, in which the polysaccharides Sl to Sn are all different from each other.

20. (Amended) The composition according to Claim 19 in which "n" is a number equal to or greater than 10.

22. (Amended) The composition according to Claim 21 in which the polysaccharides S1 to Sn are all derived from the same bacterial species.

23. (Amended) The composition according to Claim 22 in which the polysaccharides S1 to Sn are all derived from the species Streptococcus pneumoniae.

24. (New) The composition according to Claim 14 that comprises 12 to 15 conjugates.

APPLICATION SERIAL NO. 09/423,698

New and Clean Version Of Claims

1. (Amended) A composition comprising "n" conjugates C1 to Cn, wherein
   (a) each conjugate comprises
   (i) a polysaccharide S1 to Sn derived from a *Streptococcus pneumoniae* serotype/serogroup, respectively, and
   (ii) a carrier protein P1 to Pn, respectively;
   (b) "n" is a number equal to or greater than 2;
   (c) the polysaccharides S1 to Sn are identical or there are from 2 to "n" different polysaccharides; and
   (d) the carrier proteins P1 to Pn are selected independently from a group consisting of "m" carrier proteins A1 to Am, wherein "m" is a number equal to or greater than 2;
   (e) provided that at least one of the carrier proteins P1 to Pn is different from the others.

2. (Amended) The composition according to Claim 1, in which the conjugates C1 to Cn are all different from each other either by their polysaccharide, by their carrier protein, or by their polysaccharide and their carrier protein.

3. (Amended) The composition according to Claim 2, in which the polysaccharides S1 to Sn are all different from each other.

5. (Amended) The composition according to Claim 4, in which "n" is a number equal to or greater than 10.

7. (Amended) The composition according to Claim 6, in which when "n" is an even number, "n"/2 carrier proteins P1 to Pn are A1 and "n"/2 carrier proteins P1 to Pn are A2 or when "n" is an odd number, ("n"+1)/2carrier proteins P1 to Pn are A1 and ("n"-1)/2 carrier proteins P1 to Pn are A2.

9. (Amended) The composition according to Claim 8, in which the carrier proteins P1 to Pn are selected from the group consisting of Dt and Tt.

12. (Amended) The composition according to Claim 1, which comprises 10 or 11 valences represented by 10 or 11 conjugates in which the polysaccharides are all different from each other and are derived from the serotypes chosen from serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F of *S. pneumoniae*.

13. (Amended) The composition according to Claim 12, which comprises 10 or 11 conjugates selected from:

- serotype 1 polysaccharide coupled to Tt or to Dt;
- serotype 3 polysaccharide coupled to Dt;
- serotype 4 polysaccharide coupled to Tt;
- serotype 5 polysaccharide coupled to Tt or to Dt;
- serotype 6B polysaccharide coupled to Dt;
- serotype 7F polysaccharide coupled to Tt or to Dt;
- serotype 9V polysaccharide coupled to Tt;
- serotype 14 polysaccharide coupled to Dt;
- serotype 18C polysaccharide coupled to Dt;
- serotype 19F polysaccharide coupled to Tt; and
- serotype 23F polysaccharide coupled to Tt.

14. (Amended) The composition according to Claim 1that comprises 10 or 11 different polysaccharides and 12 to 22 conjugates, in which the polysaccharides are derived from the serotypes chosen from serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F and in which conjugates having the same polysaccharide differ from each other in the carrier protein.

15. (Amended) The composition according to Claim 14, which comprises:

- serotype 1 polysaccharide coupled to Tt;
- serotype 3 polysaccharide coupled to Dt;
- serotype 4 polysaccharide coupled to Tt;
- serotype 5 polysaccharide coupled to Tt;
- serotype 6B polysaccharide coupled to Dt;
- serotype 6B polysaccharide coupled to Tt;
- serotype 7F polysaccharide coupled to Tt;
- serotype 9V polysaccharide coupled to Tt;

- serotype 9V polysaccharide coupled to Dt;
- serotype 14 polysaccharide coupled to Dt;
- serotype 18C polysaccharide coupled to Dt;
- serotype 18C polysaccharide coupled to Tt;
- serotype 19F polysaccharide coupled to Tt;
- serotype 23F polysaccharide coupled to Tt; and
- serotype 23F polysaccharide coupled to Dt.

16. (Amended) A composition that comprises "n" conjugates C1 to Cn, wherein
    (a) each conjugate comprises
        (i) a polysaccharide S1 to Sn, respectively, and
        (ii) a carrier protein P1 to Pn, respectively,
    (b) "n" is a number equal to or greater than 2;
    (c) the polysaccharides S1 to Sn are identical or there are from 2 to "n" different polysaccharides; and
    (d) the carrier proteins P1 to Pn are selected independently from a group consisting of diphtheria (Dt) and tetanus (Tt) toxoids,
    (e) provided that at least one of the carrier proteins P1 to Pn is different from the others and the quantity of Dt is less than or equal to 200 and the quantity of Tt is less than or equal to 50 µg/dose.

17. (Amended) The composition according to Claim 16, in which the conjugates C1 to Cn are all different from each other either by their polysaccharide, by their carrier protein, or by their polysaccharide and their carrier protein.

18. (Amended) The composition according to Claim 17, in which the polysaccharides Sl to Sn are all different from each other.

20. (Amended) The composition according to Claim 19 in which "n" is a number equal to or greater than 10.

22. (Amended) The composition according to Claim 21 in which the polysaccharides S1 to Sn are all derived from the same bacterial species.

23. (Amended) The composition according to Claim 22 in which the polysaccharides S1 to Sn are all derived from the species Streptococcus pneumoniae.

24. (New) The composition according to Claim 14 that comprises 12 to 15 conjugates.